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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/602,272	02/16/1996	MICHAEL J. ELLIOTT	KIR96-01	4297

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JOHN P. WHITE, ESQ. COOPER & DUNHAM
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 08/21/2003

39

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n N .

08/602,272

Applicant(s)

ELLIOTT ET AL.

Examin r

Karen A Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 6,8-10,12-32 and 34-50 is/are pending in the application.
- 4a) Of the above claim(s) 16-28 and 38-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 6,8-10,12-15,29-32 and 34-37 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other: ____

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 23, 2003 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 6 and 29 have been amended. Claims 6, 8-10, 12-32 and 34-50 are pending. Claims 16-28 and 38-50, drawn to non-elected inventions, are withdrawn from consideration. Claims 6, 8-10, 12-15, 29-32, 34-37 are under consideration.

Claims 14, 15, 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are vague and indefinite in the recitation of cA2 as the only means of identifying the monoclonal antibody on which the claims depend. The use of laboratory designations only to identify a claimed antibody renders the claims indefinite because different antibodies can use the same identifiers to name completely different antibodies. Amendment of the claims to recite a deposit access number would overcome this rejection.

Claims 14, 15, 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

The specification lacks deposit information for the cA2 antibody on which the instant method claims depend. One of skill in the art must know how to make and use the claimed monoclonal antibodies and it is not clear if the exact cell line producing the antibodies can be made without undue experimentation. Although the specification references US patents on page

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8, lines 15-21 for the et al discloses how to use said monoclonals, this is not sufficient evidence that the monoclonal antibody cA2 of the instant specification will be publicly available during the enforceable life of a patent issuing from the instant application. Further, it is noted that none of the aforesaid patents (US 6,284,471, 5,656,272, 5,919,452, 5,698,195) have amended the respective specifications to reflect a Deposit number for the cA2 antibody. Thus, it appears that although said cA2 antibody has been disclosed by said patents, a deposit has not been made for patent purposes. Further, even if the aforesaid patents had made a deposit of the cA2 antibody, this is insufficient to guarantee that the cA2 antibody would be publicly available during the enforceable life of a patent issuing from the instant application.

Exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,.....no two animals, even of an inbred strain will make an identical set of antibodies." It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies.

If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance

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may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

- (a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;
- (b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;
- (c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and
- (d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibody cA2 as described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibody of cA2 as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice..

Claims 6, 8, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wakefield et al (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268) in view of Arbustini et al (American Journal of Cardiology, 1991, Vol. 68, pp. B36-B50), as evidenced by the abstract of Riipi et al (Infection and Immunity, 1990, vol. 58, pp. 2750-2754).

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Claim 6 is drawn to a method of treating or preventing thrombosis in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. Claim 29 is drawn to a method of decreasing plasma fibrinogen in a subject diagnosed as suffering from thrombosis comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to the subject. Claims 8 and 30 encompass the antagonist as an anti-tumor necrosis factor antibody or an antigen-binding fragment thereof.

Wakefield et al teach a method wherein antibodies to TNF decreased the effect of ligation of the renal vein (page 259, first column, lines 2-4, under the heading "Animal Model and Protocol" and lines 1-7 in the second full paragraph under the above heading and page 262, under the headings of "Passive Immunization Studies (Group 2))). Wakefield et al teach that TNF was elevated as a result of the ligation in rats not receiving antibodies to TNF (page 261, second column, to page 262, first column, under the heading "Cytokine Expression Within the IVC During Thrombosis" and Table 2 on page 262). Wakefield et al do not teach the administration of the anti-TNF antibodies after a "diagnosis" thrombosis as Wakefield et al actively cause the thrombosis rather than deduce the presence of thrombosis as implied by the term "diagnosis".

Arbustini et al teach that thrombosis is common in patients having unstable angina and acute myocardial infarction (page 36B, second column, lines 5-9, under the abstract and page 40B, first column lines 1-3 under the heading "Incidence of thrombosis and plaque fissuring in acute versus chronic ischemic syndromes" and page 41B, Table VI). Arbustini et al hypothesize that vascular plaques undergo fissure which can be followed by thrombus formation, and identified alpha-TNF as an endogenous cytokine which is able to "damage" atherosclerotic plaques (page 37B, first column, lines 5-24). Arbustini et al agree with other reports in the literature which teach that the amount of TNF associated with a given lesion in a artery correlates with the severity of said lesion (page 48B, second column, lines 3-11). Arbustini et al teach that alpha-TNF was not found in normal coronary arteries.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer an anti-TNF antibody to a patient having unstable angina or undergoing acute myocardial infarction.

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One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Wakefield et al which indicate that an anti-TNF antibody can attenuate thrombus induction in an experimental rat model whereby thrombosis was induced by mechanical means; and the teachings of Arbustini et al on the correlation between unstable angina and acute myocardial infarction and thrombosis, and on the further teachings of Arbustini et al which indicate the direct action of TNF to damage atherosclerotic plaques which would result in the fissuring of said plaque. Arbustini et al do not teach that all fissured plaques would necessarily produce a thrombus, however, one of skill in the art would be motivated to decrease the fissuring of any plaque in order to reduce or ablate thrombus formation, and thereby prevent arterial occlusion.

Further, the reduction of plasma fibrinogen in said subject diagnosed as suffering from thrombosis would be inherent in the method rendered obvious by the combination of Wakefield et al and Arbustini et al, as the method of decreasing plasma fibrinogen relies on the same method steps as the method of treating or preventing fibrosis. Further, the abstract of Riipi et al provides evidence that the anti-TNF antibody decreases plasma fibrinogen levels in vivo. Thus, the limitation of claim 29 and 30, drawn to a method of decreasing plasma fibrinogen are satisfied by the method rendered obvious by the combination of Wakefield et al and Arbustinti et al.

Claims 6, 8-10, 12-15, 29-32, 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wakefield et al (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268) and Arbustini et al (American Journal of Cardiology, 1991, Vol. 68, pp. B36-B50) and the abstract of Riipi et al (Infection and Immunity, 1990, vol. 58, pp. 2750-2754) as applied to claims 6, 8, 29 and 30 above, and further in view of. Le et al (US 5,656,272, cited in a previous Office action). The specific embodiments of the claims and the teachings of Wakefield et al and Arbustini et al and Riipi et al as applied to said claim limitations is set forth above.

Claims 10, 13, 32 and 35 specify the binding of the antibody to the epitopes consisting of amino acids 87-108 and 59-80 of human tumor necrosis factor. Claims 12 and 34 encompass a chimeric antibody comprising a non-human variable region specific for TNF and a human

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constant region. Claims 14 and 36 specify that the chimeric antibody inhibits the binding of TNF-alpha to the monoclonal antibody cA2. Claims 15 and 37 specify that the chimeric monoclonal antibody is cA2.

Le et al teach that the chimeric monoclonal antibody cA2 recognizes two peptide sequences of TNF-alpha consisting of the fragments defined by amino acids 87-108, and amino acids 87-108. Further, Le et al teach antibodies which compete with cA2 for binding to TNF-alpha (column 11, lines 39-50) and methods for obtaining said antibodies (column 17, lines 57-67), thus disclosing the embodiments of claims 14 and 36. Le et al teach that the administration of the chimeric version of the murine antibodies to humans overcomes the problems of murine antibody immunogenicity and provides increased TNF neutralization activity (column 5, lines 19-22).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the cA2 antibody to a patient having unstable angina or undergoing acute myocardial infarction.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Le et al on the improvements of avoiding anti-murine anti-antibody response in human patients and the subsequent increase in antibody neutralization activity afforded by the administration of the cA2 antibody rather than a murine anti-TNF antibody.

Claims 6, 8, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wakefield et al (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268) in view of Arbustini et al (American Journal of Cardiology, 1991, Vol. 68, pp. B36-B50) and Esser (WO 92/09203), as evidenced by the abstract of Riipi et al (Infection and Immunity, 1990, vol. 58, pp. 2750-2754) as applied to claims 6, 8, 29 and 30 above, and further in view of Esser (WO 92/09203).

The specific embodiments of the claims and the teachings of Wakefield et al and Arbustini et al and Riipi et al as applied to said claim limitations is set forth above. It is noted that claims 6 and 29 are broadly drawn to tumor necrosis factor antagonists and thus encompass

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methods comprising the administration of molecules which are broader in scope than anti-TNF antibodies.

Esser teaches the administration of inhibitors of TNF (for example, claim 1) for the treatment of diseases mediated by TNF (page 6, lines 1-7). Esser teaches that the disease state can be a result of recessive or unregulated TNF production in a human (page 11, line 31 to page 12, line 4). Esser notes that TNF is a likely mediator of tissue injury in myocardial infarction and stroke. It is noted that Arbustinti et al teaches that thrombosis is common in patients having acute myocardial infarction.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the inhibitors of TNF as taught by Esser to a patient having unstable angina or undergoing acute myocardial infarction.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Wakefield and Arbustini et al who link elevated levels of TNF with thrombosis. Esser does not specifically teach that the TNF inhibitors are antagonists of TNF, however, the specification states on page 3, lines 2-5, that the TNF antagonists include compounds which prevent or inhibit TNF synthesis or release. Esser teaches that the THNF inhibitors inhibit the production of TNF by human monocytes, thus fulfilling the definition of TNF antagonist as set forth in the specification.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentable distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. *In re Berg*, 140 F. 3d 1428, 46 USPQ2d 1226 (Fed Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Claims 6, 8-10, 12-15, 29-32, 34-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/598,079 and claims 1-23 of copending Application No. 09/754,004 and claims 32-54 of copending Application No. 09/921,937 and claims 1-20 of copending Application No. 10/252,489, all in view of Wakefield et al (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pp. 258-268) and Arbustini et al (American Journal of Cardiology, 1991, Vol. 68, pp. B36-B50) as evidenced by the abstract of Riipi et al (Infection and Immunity, 1990, vol. 58, pp. 2750-2754). Claims 1-15 of the '079 application are drawn to methods of treating or preventing a tumor necrosis factor disease comprising the administration of a tumor necrosis factor antagonist, claims 1-23 of the '004 application are drawn to methods of treating a tumor necrosis factor mediated disease in an individual in need thereof comprising the administration of methotrexate and a tumor necrosis factor antagonist, claims 32-54 of the '937 application are drawn to a method for the treating or preventing a tumor necrosis factor-mediated disease in an individual in need thereof comprising co-administration of methotrexate and a tumor necrosis factor antagonist to said individual in a therapeutically effective amount; claims 1-20 of the '489 application are drawn to a method of treating reoccurrence of a TNF-mediated disease in an individual having the TNF-mediated disease comprising the administration of multiple treatment cycles of anti-TNF antibody to said individual, wherein each treatment cycle is administered after loss of response to the previous cycle has occurred. All of these claims teach a method of treating TNF-mediated diseases. The

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claims to not teach thrombosis as a specific-TNF-mediated disease or the decrease of plasma fibrinogen levels by the administration of a TNF antagonist..

Wakefield et al teach thrombosis as a TNF-mediated disease because inhibition of the activity of TNF abrogates thrombosis in a rat experimental model.

Arbustini et al teach that TNF can damage plaques leading to fission and thrombosis and that TNF is not detected in normal arteries. Arbustini et al teach that thrombosis is characteristic of patients having unstable angina and acute myocardial infarction.

The abstract of Riipi et al teaches that the administration of anti-TNF antibodies decreases plasma fibrinogen levels, and thus is inherent in the administration of said antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to carry out the methods of claims 1-15 of the '079 application or claims 1-23 of the '004 application or claims 32-54 of the '937 application or claims 1-20 of the '489 application to treat thrombosis in a patient having unstable angina or undergoing acute myocardial infarction.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Wakefield and Arbustini et al who link elevated levels of TNF with thrombosis and link thrombosis with acute myocardial infarction and unstable angina. Further, it would be inherent in the methods of claims 1-23 of the '004 application or claims 32-54 of the '937 application or claims 1-20 of the '489 application that the level of plasma fibrinogen would be decreased in said patients, as this is an inherent property of the claimed method which is evidenced by the abstract of Riibi et al that teaches an decrease in plasma fibrinogen levels after administration of an anti-TNF antibody.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may

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be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

August 11, 2003